455.1005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re:	Application of:	HASHMI, Syed, et al.
	Serial No.:	10/031,581
	Filed:	January 18, 2002
	For:	**COMPOSITIONS ADDRESSING INFLAMMATION AND/OR DEGENERATIVE DISORDERS**
	Examiner:	Shenjun Wang
	Art Unit:	1617

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

DECLARATION OF SABINA A. HOLLE UNDER 37 C.F.R. § 1.132

I, Sabina A. Holle, hereby declare that:

1. I received an M.D. in veterinary science (Veterinary Surgeon) from the Justus Liebig University in Giessen, German in 1987, and received a Ph.D. in Veterinary Science from Massey University in Palmerston North, New Zealand in 1992.

2. Between 1992 and 1997, I completed postdoctoral research at Massey University in veterinary pathology and equine clinical science. Between 1998 and 2002, I tutored at Massey University and Waikato Polytechnic University in equine studies, heading the program at Waikato Polytechnic University. In 2003, I joined Bomac Research Ltd., the Assignee of the above-identified application, as a research veterinarian.

3. I submit this declaration in support of a Response to the Office Action dated September 28, 2004 from the U.S. Patent and Trademark Office in connection with the above-

identified application. I submit this declaration in order to help demonstrate that amended claims 1, 5, 9, 12, 15-19, 22 and 35-38 of the application are, in fact, patentable.

4. I understand that the composition claimed in amended claims 1, 5, 9, 12, 15-19, 22 and 35-38 that are pending in this application (as a result of amendments in the Response filed herewith) are directed towards the Assignee's main commercial embodiment for the composition. I understand that the invention as claimed in these amended claims relates to the surprisingly enhanced therapeutic effects obtained from administration of the claimed composition ("the claimed composition") over the therapeutic effects expected from administration of the individual components of the claimed composition alone.

5. My understanding is based upon certain recent experiments and trials, of which I was the Sponsor Representative and Trial Monitor, which proved that the improved effect noted in trials referred to in the specification are indeed correct. Substantially improved joint health was noted from administration of the claimed composition in the trials as discussed below.

6. The clinical trial was conducted to evaluate the efficacy of the claimed composition in dogs showing various degrees of lameness and vertebral stiffness. The study was also intended to determine the efficacy of the claimed composition as an alternative to non-steroidal anti-inflammatory drugs for the ongoing maintenance treatment of chronic lameness in dogs. If the study was deemed successful, the claimed composition could be offered to dogs with mild to moderate lameness and osteoarthritis and also to those that have previously been treated with combination of non-steroidal anti-inflammatory drugs and the claimed composition during the acute phase, as a long term therapeutic alternative, without the negative side effects associated with treatment by non-steroidal anti-inflammatory drugs.

7. The trial was initiated during the second part of 2004 as a double blind, placebo-controlled multi-center field study, according to a blocked randomized design conducted at up to ten small animal clinics based in the North and Upper South Islands, New Zealand. From the regular client base of each clinic (a total of up to 150 dogs were prescreened initially), dogs were screened for possible inclusion into this study. The final number of selected dogs was based on

specified inclusion criteria. From the pre-screened group, animals were allocated into various groups that received different medication during the initial 12-week study period.

8. Below, I report on early results from a small subset of dogs that were given tablets comprising the claimed composition as compared to dogs without any treatment. Data was collected from a client questionnaire and by kinematic gait analysis from dog gaits recorded on videotape. The first data set represents a subjective measure of dog owners' perceptions of possible improvement of their dogs over time, whereas the second data set is considered an objective, quantitative analysis of gait improvement.

9. At the end of the 12-week study period, dogs remained enrolled in the study until week 52, at which time a final clinical exam was conducted. Data on the progress of the dogs during the 12-week study period was collected at various intervals, namely weekly for client questionnaires, every three weeks for clinical exams and every six weeks for video recordings of dog gaits.

10. With respect to the data collected from a client questionnaire, information was collected by dog owners, who assessed the effects of treatment on the dogs' mobility by weekly observation of their dogs and completion of a questionnaire. Dog owners were asked to monitor any changes in the overall mobility of their dog(s), by rating eight common activities on a five-point scale. Total mobility scores were calculated per week, and changes were expressed as percentage change, i.e., improvement or deterioration.

11. Table 1 below summarizes the observed changes of dogs that were treated with the claimed composition versus dogs that were treated with a placebo (sugar tablet) over the first six weeks of the trial. Changes are expressed as total number of dogs showing improvement, as well as broken down further into intervals of percentage improvement.

Table 1: Improvement in Total Mobility Score in Dogs Receiving the Claimed Composition or a Placebo for 6 Weeks

	Claimed Composition	Placebo Control
<0% increased score	1	4
no change	2	1
< 10%	4	2
10-20%	5	1
21-30%	2	2
31-40%	2	1
41-50%	0	0
>50%	3	0
Total Number of Dogs	**19**	**11**
Total Improved	**16**	**6**
Unchanged & Improved	**18**	**7**
% Improved	**84.2**	**54.5**
% Unchanged & Improved	**94.7**	**63.6**

Early results (Table 1) indicate that about 84% of dogs showed a visible improvement in their mobility when given the claimed composition, compared with only 54% in the placebo group, as perceived by their owners.

12. In addition, dogs that previously received a placebo were switched to the claimed composition after week 6 for the remainder of the twelve-week initial study period. As shown in Table 2 below, these dogs also showed a 75% improvement, and none of the dogs were perceived to deteriorate, whereas, during the initial six weeks on placebo treatment, four out of eleven dogs were reported to show deterioration. Compared to this result, 62% of a subset of the group of dogs that had received the claimed composition from the start of the trial showed further improvement during weeks 7-12.

Table 2: Improvement in Total Mobility Score in Dogs receiving the Claimed Composition for 12 Weeks or 6 Weeks (former Placebo Group)

	Claimed Composition 12 weeks (Weeks 7-12)	Former Placebo Group Now Claimed Composition
<0% increased score	1	0
no change	2	2
< 10%	1	1
10-20%	3	3
21-30%	1	0
31-40%	0	0
41-50%	0	0
>50%	0	2
Total Number of Dogs	**8**	**8**
Total Improved	**5**	**6**
Unchanged & Improved	**7**	**8**
% Improved	**62.5**	**75**
% Unchanged & Improved	**87.5**	**100**

Given the small number of dogs that make up this specific data set and the subjective nature of questionnaires, often leading to a 25-30% error (due to lack of objectivity in assessing ones own dog and the "placebo effect" recognized in the scientific literature), this is still a promising result, indicating the potential efficacy of the claimed composition.

13. With respect to the data collected from kinematic dog gait analysis, dogs enrolled into the study were videotaped at weeks 0, 6 and 12, according to a protocol that specified the location and length of the run path between markers, which were set at a pre-determined distance to a stationary video camera. After calibration of the run path, dogs were equipped with reflective markers over prominent boney points on their legs and trunk. Videos were then recorded and later captured and analyzed using a specialized computer software program. Preliminary results on some extracted parameters of two dogs that received the claimed composition over twelve weeks show an obvious improvement.

14. As the first parameter of improved mobility of the dogs, the tuber coxae (hip joints) was chosen, since it reflects the summation of all possible problems that a dog could exhibit in its hind legs. The minimization of vertical displacement around the center of gravity is

a measure of a more efficient gait in quadruped animals and can be taken as an indication of lameness reduction. As shown in Table 3 below, the results show that the values for the variation around the trajectory of the tuber coxae, or the vertical displacement along the run path, decrease during the claimed composition treatment period. This means that the dog was able to show a much smoother trotting gait at the end of the trial than at the beginning.

Table 3: Mean variation (cm) around the trajectory of the Tuber coxae (hip bone).

Dog ID	Week 0	Week 6	Week 12
3	1.85	1.77	0.85
8	2.07	2.10	0.88

15. The second parameter of improved mobility of the dogs is the variation around the trajectory of the nose. This parameter is chosen because, in quadruped animals, any limb lameness is usually associated with abnormal movement of the head. For this dataset, each dog is taken as its own control. The typical gait of a healthy dog without problems is expected to show consistent values over the observation times. Similarly, a lack of response to treatment would either record similar values as those recorded at the beginning of the trial or show up higher values due to further deterioration in the mobility of the dog. Again, as shown in Table 4 below, using this parameter, the results showed an improvement of the vertical displacement of the nose (head) with time of treatment.

Table 4: Mean variation (cm) around the trajectory of the Nose.

Dog ID	Week 0	Week 6	Week 12
3	3.39	2.45	0.12
8	5.79	2.45	1.62

16. In summary, my interpretation, based upon the preliminary results obtained from a small subset of data collected from subjective client questionnaires and quantitative kinematic data from video analysis of dog gaits, is that there were obvious improvements in the mobility and in the degree of lameness in dogs that received the claimed composition over a six- and twelve- week period. Accordingly, I believe that the trial information discussed above backs up data in the patent specification that the combination of agents used in the composition shows a

positive effect in reducing lameness (possibly due to decrease of inflammation) and increasing joint mobility of dogs.

I hereby declare that I understand the English language and that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued therefrom.

Sabina A. Holle, M.D., Ph.D.

Dated: Auckland, New Zealand
March 28, 2005